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Intraoperative Electron Beam Radiotherapy in Recurrent Colorectal Carcinoma

SUBIR NAG, MD,[1]* RAFAEL MARTINEZ-MONGE, MD,[1] AND EDWARD W. MARTIN, MD,[2]
[1]Division of Radiation Oncology, Arthur G. James Cancer Hospital and Research Institute, The Ohio State University, Columbus, Ohio
[2]Division of Surgical Oncology, Arthur G. James Cancer Hospital and Research Institute, The Ohio State University, Columbus, Ohio

Background and Objectives: The installation of a dedicated linear accelerator in a shielded operating room in 1992 allowed us to start a feasibility study of intraoperative electron beam radiation therapy (IOERT) in colorectal carcinoma.

Methods: From March 1992 to February 1996, 28 patients with recurrent colorectal carcinoma were treated with maximal surgical resection and IOERT to the pelvis ($n = 20$) or paraortics ($n = 8$). IOERT dose ranged from 10 to 20 Gy with electron energies of 6–15 MeV. Postoperative external beam radiation therapy (EBRT) of 45–50 Gy was planned for the previously unirradiated patients.

Results: IOERT was well tolerated, but 10 (70%) of 13 patients in the previously unirradiated group did not complete the EBRT per protocol. Eight patients (29%) had some morbidity including surgically related fistula distal from IOERT sites. Two patients developed pelvic pain, which can be attributed to IOERT. Three-year local control at sites treated with IOERT was 40% (53% for previously irradiated patients and 27% for previously unirradiated patients). The 3-year actuarial overall survival was 12% (17% for previously irradiated patients and 8% for previously unirradiated patients).

Conclusions: Our initial experience showed that it was feasible to treat poor prognostic colorectal cancer patients with IOERT. The morbidity observed was mainly related to extensive surgery in high-risk patients. Poor local control was obtained in patients treated with low-dose IOERT alone. Hence, previously unirradiated patients are encouraged to complete the planned EBRT or, alternatively, are considered for EBRT preoperatively or are given a higher IOERT dose (up to 20 Gy) if EBRT will not be given. Since IORT doses >20 Gy are associated with nerve toxicity, we currently add limited dose EBRT in the previously irradiated group. Patients with disease located in multiple abdominal sites are no longer considered candidates for IOERT.

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KEY WORDS: colorectal neoplasms; surgery; radiotherapy; intraoperative period; complications; particle accelerators

INTRODUCTION

Locally recurrent colorectal cancer represents a difficult clinical problem. Salvage surgery is the preferred treatment option, but unresectability is the rule, due to invasion of bone, major vessels, or nerves. Furthermore,

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*Correspondence to: Subir Nag, MD, Chief of Brachytherapy, Arthur G. James Cancer Hospital, Ohio State University, 300 W. Tenth Ave., Columbus, OH 43210. Fax No.: (614) 293-4044.
E-mail: nag.1@osu.edu

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chemotherapy and external beam radiation therapy (EBRT) have limited value since they have been used before during the management of the primary disease. For all these reasons, only a few patients with locally recurrent colorectal carcinoma are expected to achieve long-term disease-free survival. Clearly, alternative treatment strategies have to be sought.

Intraoperative electron beam radiation therapy (IOERT) has the advantage of direct tumor visualization and ability to displace or shield surrounding normal tissues away from the irradiated volume, thus potentially reducing morbidity. IOERT has been used in the management of recurrent colorectal cancer for more than a decade [1–5]. Installation of a dedicated linear accelerator in a shielded operating room in 1992 allowed us to start a feasibility study of IOERT for colorectal cancer. Since there have been reports of toxicity with the use of IOERT doses, we elected to begin our new IOERT program with a dose escalation trial to evaluate feasibility and morbidity. Our technique and preliminary clinical results have been only partially reported as part of larger series [6,7]. This article is a definitive report of the IOERT experience at Ohio State University.

MATERIALS AND METHODS

Twenty-eight patients (15 men, 13 women; ages 35–79 years; mean 58 years) were treated with IOERT between March 1992 and February 1996. All patients had recurrent disease after surgery. In addition, 15 patients (54%) had received prior radiation therapy to the areas treated with IOERT. Twenty-five patients (89%) had received chemotherapy, usually 5-fluorouracil (5-FU) alone or in combination, during the management of the primary disease or after relapse (Table I). Thirteen patients had isolated relapses confined to the pelvis or paraortic nodes, and 15 also had low-volume metastatic disease that had been resected prior to IOERT. At our institution, patients with recurrent colorectal cancers and no demonstrable extra-abdominal disease are managed aggressively by surgery, even if they have metastatic disease, due to the availability of radioimmunoguided surgery (RIGS), which allows detection of subclinical metastatic disease [8,9]. Twenty-two of 28 patients underwent surgery under RIGS (79%).

The technical details of IOERT have been previously described [6,7] and will be only briefly outlined here. After determination of the target volume, adjacent normal tissue was excluded from the field by retraction and/or by packing with gauze. The IOERT applicator could also aid in keeping radiosensitive structures out of the field. Normal tissues that could not be retracted (e.g., nerves or kidneys) were shielded by pliable lead sheets if not thought to contain tumor. Occasionally, adjacent tumor tissue could be manipulated and brought into the radiation field. We used a soft-docking system, that is, the linear accelerator was not directly connected to the IOERT applicator. The applicator was positioned over the tumor bed and was lined up with the radiation beam using laser alignment. The overall time for the IOERT procedure was 30–45 min, including the actual treatment of 3–5 min.

TABLE I. Characteristics of Colorectal Cancer Patients Treated With IOERT

	Previously irradiated	Previously unirradiated	Total
No. of patients	15	13	28
Previous treatment			
Surgery	15	13	28
Laparotomies, mean	2.1	1.6	1.8
Radiation therapy[a]	15	—	15
Chemotherapy	15	10	25
Initial location			
Ileum	1	—	1
Cecum/ascending colon	1	5	6
Transverse colon	1	1	2
Descending colon/sigmoid	1	6	7
Rectosigmoid	3	—	3
Rectum	7	1	8
Colon remnant	1	—	1
Clinical presentation			
Pelvic or para-aortic relapse	9	4	13
Pelvic or para-aortic relapse + distant metastasis	6	9	15
Surgical procedure			
Exenteration, partial or total	4	4	8
Abdominoperineal reection/colectomy	1	2	3
Hartman's procedure	—	1	1
Colectomy + liver resection	1	1	2
Nodal resection	2	5	7
Debulking procedures	7	—	7
Tumor residual			
Microscopic/close margins	6	9	15
Gross	9	4	13
Adjuvant treatment: postoperative radiotherapy	1	5	6

[a]In areas treated later with IOERT. Two additional patients had received prior radiation to areas that were not treated with IOERT.

Two different treatment protocols were used in the management of these patients. Fifteen patients who had received prior radiation therapy were treated with IOERT alone to a total dose of 15 Gy (prescribed to the 90% isodose line) for close margins (<1 cm) or microscopic residual disease and 17.5–20 Gy for gross residual disease. Thirteen patients who had not received prior radiation were treated with IOERT doses of 10 Gy for close or microscopically involved margins and 15 Gy for gross residual disease, with supplementary postoperative conventional EBRT of 45–50 Gy planned. The details of IOERT are given in Table II.

Treatment results were estimated according to the Kaplan and Meier method and compared using the log-

TABLE II. IOERT Parameters of the Colorectal Cancer Patients Treated

	Previously irradiated	Previously unirradiated	Total
IOERT site			
Pelvic	11	9	20
Para-aortic	4	4	8
Dose (Gy; median 15 Gy)			
10.0	—	10	10
15.0	8	3	11
17.5	3	—	3
20.0	4	—	4
Applicator diameter (cm; median 7 cm)			
5–6	3	7	10
7–8	9	6	15
9	3	—	3
Applicator type			
Flat	8	4	12
Beveled	7	9	16
Electron energy (MeV)			
6	4	6	10
9	5	4	9
12	2	2	4
15	4	1	5

rank test [10]. Patient characteristics (sex, initial tumor location, clinical presentation) and treatment factors (IOERT site and dose, tumor residual, postoperative radiation therapy, use of radioimmunoconjugates to guide surgery, and IOERT) were analyzed using local failure and overall survival as end points.

Local failure was defined as relapse or regrowth of malignant tumor within the area treated with IOERT. Twenty-one patients (75%) were fully evaluable. Seven patients were considered nonevaluable for local failure. Of these, 5 died within the first 4 months of follow-up and 2 had insufficient follow-up information.

RESULTS

Morbidity

Eight patients (29%) suffered some morbidity; the complications were severe in 4 (14%). A complete description of the complications observed is provided in Table III. In the group of previously irradiated patients (n = 15), 3 cases of fistula were observed (20%). One patient developed a urinary fistula in the immediate postoperative period and died of multiple organ failure during the first month. Another patient developed a recurrent enterovaginal fistula that was surgically repaired on several occasions. This patient eventually died of her enteric fistula without evidence of recurrent disease at 24 months. Another patient developed an enterocutaneous fistula that was successfully repaired. Two patients developed postoperative pelvic pain probably related to IOERT. In the group of previously unirradiated patients (n = 13), 1 case of enteric fistula was observed (8%). This patient died of multiple organ failure at 3 months.

TABLE III. Morbidity Observed in Colorectal Cancer Patients Treated With IOERT

	Previously irradiated	Previously unirradiated	Total
Total no. of patients treated	15	13	28
No. of patients with severe morbidity	3 (20%)	1 (8%)	4 (14%)
Urinary fistula	1	—	1
Myocardial infarction	1	—	1
Enteric fistula	2	1	3
Deep venous thrombosis	1	—	1
Pelvic pain	2	—	2
Short gut syndrome	1	1	2
Abdominal wall abscess	—	1	1

Local Control

In the previously irradiated patients, the 3-year actuarial local control rate was 53% (median not reached). Details are provided in Table IV. In the previously unirradiated patients, the 3-year local control was only 27%, and the median time to local failure was 9 months (95% CI: 3–15 months). Only 3 of 10 evaluable patients actually had their disease controlled. In this later group, 8 patients did not receive any of the planned EBRT due to noncompliance (6) or poor performance status (2). Two additional patients started but did not complete the planned EBRT due to poor tolerance; the prescribed radiation courses were terminated at 21 and 36 Gy. Hence, only 3 patients in this group completed the prescribed EBRT. A summary of factors predicting an improved local control and survival is displayed in Table V.

Overall Survival

In the previously irradiated patients, the 3-year actuarial overall survival was 17%, with a median overall survival of 21 months (95% CI: 15–27 months). In the previously unirradiated patients, the 3-year actuarial overall survival was 8%, with a median overall survival of 15 months (95% CI: 9–22 months).

DISCUSSION

Morbidity

The main concern in IOERT trials for recurrent colorectal cancer is the high incidence of severe surgical complications. The overall incidence of complications in the literature is in the 20%–40% range [1–5]. Four of 28 patients (14%) developed severe complications in the present series. These are the consequence of very extensive surgical resection and anastomosis of areas previ-

TABLE IV. Three-Year Actuarial Results (%) of Colorectal Cancer Patients Treated With IOERT*

	Local control			Survival		
	Previously irradiated	Previously unirradiated	Overall	Previously irradiated	Previously unirradiated	Overall
All patients	53	27	40	17	8	12
Location						
Para-aortic	100	37	56	50	25	31
Presacral	57	—	45	15	0	7
Lateral pelvis	—	—	—	—	—	—
Residual disease						
Gross	50	—	33	15	0	9
Microscopic	53	37	43	22	11	15
EBRT						
Completed	NA	33	33	NA	33	33
Not completed	NA	—	40	NA	0	10
RIGS						
RIGS-directed	71	27	44	23	8	15
Not RIGS-directed	—	NA	—	—	NA	—

*NA, not applicable.

TABLE V. Factors Predicting Improved Outcome of Colorectal Patients Treated With IOERT*

	P[a]		
	Previously irradiated	Previously unirradiated	Overall
Local control			
Use of RIGS	NS	—	—
Para-aortic location	0.001	NS	0.02
No side-wall involvement	0.001	NS	0.02
Microscopic residual at the IOERT site	NS	NS	NS
Survival			
Use of RIGS	0.03	0.0005	0.01
Para-aortic location	NS	0.03	0.007
No side-wall involvement	0.04	0.05	0.007
Microscopic residual at the IOERT site	NS	NS	NS
Postoperative EBRT	—	0.002	NS

*NS, not statistically significant.
[a]Obtained through the log-rank test.

ously treated with one or more surgical procedures, sometimes with additional chemoradiation. The rate of severe complications directly associated with IOERT (neuropathy and sacral necrosis) is in the 1%–10% range. This has been associated with higher IOERT doses and beam energies. In the present series, only 2 cases of pelvic pain could be attributed to IOERT (Table III).

It is difficult to clearly separate treatment-related complications from disease-related complications in patients with recurrent colorectal cancers. Complications such as delayed healing, infection, fistula, and neuropathy may be the result of recurrent tumor, aggressive surgery, radiation, or a combination of these. The complication rate observed in this series is high but not essentially different from those reported in other IOERT series for recurrent colorectal cancer. Most of the morbidity noted was surgery related and comparable to the morbidity seen in the patients treated with surgery alone.

Factors Influencing Outcome

Most series report better local control and survival for previously unirradiated patients compared to that seen with previously irradiated patients [1–5]. In the present study, the previously unirradiated patients had poor local control (3-year actuarial local control of 27% and a median control time of 9 months). The most likely reason for the poor result is that these patients received a lower IOERT dose because postoperative EBRT was planned; however, only 3 (23%) of 13 patients actually completed the planned EBRT. A single IOERT dose of 10 Gy is radiobiologically equivalent (using $\alpha/\beta = 10$) to 17 Gy fractionated radiation in terms of tumor effect [11]. This

dose cannot be expected to control even microscopic disease; this probably explains the poor local control and survival of these patients.

Various factors contributed to the poor compliance rate. Some of these patients were in poor medical condition, often suffering high morbidity after extensive surgery, and were not EBRT candidates. Since our institution is a tertiary referral center, the patients were often referred here for the specialized treatments that were not locally available in their home towns, where the EBRT was often given. Some of the referring physicians may have been reluctant to subject patients with metastatic disease to EBRT. Many patients lived far from radiation oncology centers and were unable to travel long distances for daily treatments. Some patients and referring physicians may not have been convinced that even though these patients had received radiation intraoperatively, they needed further EBRT.

On the basis of this experience, we now emphasize to the patients and the referring physicians that EBRT must be completed. Another strategy is to deliver the EBRT preoperatively for patients with isolated pelvic or paraortic recurrences. The preoperative setting offers the advantage that most of the patients will receive the prescribed radiation dose. An additional advantage is that IOERT can be avoided in patients presenting with progressive disease before surgery. In patients who will not be able to receive supplementary EBRT, a higher dose of IOERT (20 Gy) is considered if the underlying normal tissues will tolerate it.

Gunderson et al. [12] have shown improvement in local control with the addition of EBRT to IOERT in previously irradiated patients. In an attempt to improve the local control rates for these patients, our current policy is to deliver additional low-dose (20–30 Gy) postoperative EBRT for previously irradiated patients.

Other factors significantly affect the outcome of these patients. It has been shown that patients presenting with microscopic residual disease fare better than those with gross residual disease [1–5]. A similar trend is seen in the present series. The patients with microscopic residual disease had a better local control (43% vs. 33%) and survival (15% vs. 9%) compared to the patients with gross residual disease. The difference was not statistically significant, probably due to the lack of adjuvant EBRT in a significant percentage of patients.

The location of the recurrent disease affected the outcome (Table V); those with para-aortic disease fared better than those with pelvic disease. Patients with pelvic side-wall involvement constituted an extremely unfavorable group. One possible explanation for the improved local control and survival found in the patients with para-aortic metastases is that these patients had well localized, small volume recurrent tumors that could be resected with limited surgery and minimal morbidity and could be well encompassed by the IOERT applicator.

Another consideration is the presence of distant metastases that, although completely resected, lie beyond the IOERT treatment area and are not treatable with an adjuvant postoperative EBRT field. In our study, 5 of the 7 patients who survived >2 years had isolated pelvic or para-aortic relapses. Only 2 of the 15 patients presenting with distant metastases survived beyond 2 years. Hence, IOERT should be discouraged in patients presenting with multiple metastatic sites, especially if both the upper abdomen and pelvis are involved.

Finally, 22 of 28 patients had RIGS-directed surgery. These patients had better local control (44% vs. 0%) and survival (15% vs. 0%) compared to that seen in patients who did not have RIGS-directed surgery. However, it must be noted that the subset numbers are small and further, 3 patients in the non-RIGS series had pelvic sidewall involvement, which is a poor prognostic factor.

CONCLUSIONS

Our initial experience showed that it was feasible to treat colorectal cancer patients with poor prognosis with IOERT. The morbidity observed was mainly related to extensive surgery in high-risk patients. Poor local control was obtained in patients treated with low-dose IOERT alone. Hence, previously unirradiated patients are encouraged to complete the planned EBRT or alternatively, are considered for EBRT preoperatively or are given a higher IOERT dose (up to 20 Gy) if EBRT will not be given. Since IORT doses >20 Gy are associated with nerve toxicity, we currently add limited-dose EBRT in the previously irradiated group. Patients with disease in multiple abdominal sites are no longer considered candidates for IOERT.

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